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PHYSIOLOGICAL SIGNIFICANCE OF THE SWEAT RESPONSE TO ADRENALINE IN MAN

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In his classic paper on the actions of adrenaline Elliott (1905) reported that human sweat glands were not excited by this substance. When Dale & Feldberg (1934) showed that the nerve supply to the sweat glands of the cat's footpad was cholinergic in type, the responsiveness of these glands to substances with muscarinic properties and the inhibition of secretion by atropine were readily explained. However, it has recently been shown by Kisin (1948), Sonnenschein, Kobrin & Grossman (1949), Haimovici (1950) and Wada (1950) that in most human subjects the sweat glands do respond to adrenaline, and Haimovici (1948, 1950) has indeed suggested that in man the glands may receive an adrenergic as well as a cholinergic innervation.

In this paper we describe experiments designed to determine the possible physiological significance of the sweat secretion evoked by adrenaline in man. Our observations have already been briefly reported (Chalmers & Keele, 1951).

METHODS

For the detection of sweating we have used an iodine-starch paper test (Randall, 1946), in which the skin is painted with 3% iodine in 95% alcohol and a piece of starch paper applied for ½ min. to the test area: each active sweat gland imprints a dark blue dot on the paper. The secretory responses to locally injected L-adrenaline tartrate and hydrochloride, DL-noradrenaline hydrochloride, ephedrine hydrochloride and acetylcholine chloride were studied. The drugs were dissolved in sterile normal saline and the concentrations are expressed in g./ml. of solution. The volume of injected solution was 0·01–0·05 ml. Atropine sulphate and the anti-adrenaline drugs dibenamine hydrochloride, dihydroergotamine tartrate (DHO), dihydroergocristine tartrate, piperoxane hydrochloride (933F) and tolazoline hydrochloride (Priscol) were introduced into the skin by intradermal injection or, in some cases, by iontophoresis (an electric current of 1 mA./cm.^{2} being passed for 10 min. through a skin pad soaked in a 10^{-3} or 10^{-4} solution of the drug).

RESULTS

Responses to adrenaline

Adrenaline was injected intradermally in the forearm in thirteen normal young adults. In eleven there was a local secretion of sweat at the site of injection: the smallest effective (i.e. threshold) concentration of adrenaline varied from

10^{-3} to 10^{-7} in different subjects. In only two subjects was there no secretory response to 10^{-3} adrenaline. Sweating was detectable within 30 sec. of the injection and persisted for up to an hour. In some subjects secretion was also elicited by noradrenaline, and a comparison of the threshold concentrations of adrenaline, noradrenaline and acetylcholine is shown in Table 1. It can be seen that sensitivity to the three drugs ran more or less parallel. There was, however, a difference in the rate of secretion of sweat as judged by the size of the dots on the starch paper, which were larger with acetylcholine than with the two vascoconstrictor drugs.

TABLE 1. Sweat responses to locally injected adrenaline, noradrenaline, and acetylcholine in man

(The figures in the table show the smallest effective concentrations (in g./ml.) found to produce sweating on intradermal injection in the forearm. Sweating was detected by the iodine-starch paper method.)

Subject	L-Adrenaline	DL-Noradrenaline	Acetylcholine
D.H.H.	No response	No response	No response
J.B.L.H.	No response	—	10^{-3}
J.O.	10^{-3}	No response	10^{-3}
C.A.K.	10^{-3}	10^{-3}	10^{-4}
G.M.	10^{-4}	10^{-4}	10^{-4}
M.K.M.	10^{-4}	—	10^{-4}
G.S.	10^{-5}	—	10^{-4}
A.A.G.L.	10^{-5}	—	10^{-5}
F.H.	10^{-5}	—	10^{-6}
E.P.S.	10^{-6}	10^{-4}	10^{-5}
J.M.	10^{-6}	—	10^{-5}
G.L.S.P.	10^{-7}	10^{-6}	5×10^{-6}
T.M.C.	10^{-7}	—	10^{-7}

No response = no response to 10^{-3}. — = no observation.

The response of the palmar sweat glands to adrenaline was also tested. After elimination of spontaneous sweating by procaine block of the median nerve at the wrist, a well-marked secretion of sweat was obtained at the site of injection of 10^{-4} to 10^{-6} adrenaline in three individuals. Acetylcholine, of course, also stimulates the palmar glands (Chalmers & Keele, 1949).

Systemic administration of adrenaline did not produce detectable sweating. A subject who consistently showed a local sweat response to intradermal injection of 10^{-7} adrenaline was given the drug by slow intravenous infusion at various rates up to 15 μg./min. without sweating. Intra-arterial (brachial) injections also failed to stimulate the sweat glands, although as much as 20 μg. was rapidly injected, both in this subject and in another whose sensitivity to intradermally injected adrenaline was slightly less.

Ephedrine (1:300) was injected intradermally in two subjects, who were sensitive to intradermal adrenaline. No sweat response could be detected to ephedrine alone, and no potentiation of the adrenaline response was observed.

Local introduction of atropine into the skin (0·2 ml. of a 10^{-4} solution) prevented acetylcholine but not adrenaline responses. Adrenaline blocking agents, in suitable concentrations, selectively inhibited the adrenaline response

(Table 2). In all cases the blocking agent was injected 10–15 min. before the stimulant drug.

TABLE 2. Effect of prior intradermal injection of adrenaline-blocking agents on sweat responses to locally injected adrenaline and acetylcholine

		Degree of inhibition			
		Adrenaline			Acetylcholine
Blocking agent	Concentration	10^{-6}	10^{-5}	10^{-4}	10^{-4}
Dihydroergotamine	10^{-6}	2	—	1	0
	10^{-5}	3	—	1	0
	10^{-4}	3	—	2	2
Dihydroergocristine	10^{-4}	3	0	—	—
Dibenamine	10^{-3}	2	—	0	—
Benzodioxane (933F)	10^{-3}	—	0	0	—
Priscol	10^{-5}	—	—	0	—
	10^{-4}	—	2	0	—
	10^{-3}	—	—	2	0
	10^{-2}	3	—	2	1

3 = complete inhibition of sweat response; 2 = marked inhibition of sweat response; 1 = slight inhibition of sweat response; 0 = no inhibition of sweat response; — = not tested. Volume of solution of blocking agent was 0·2 ml. Volume of solution of adrenaline or acetylcholine was 0·05 ml. Drug concentrations in g./ml.

Adrenaline inhibitors and atropine on reflex sweating

The effect of blocking agents on nervously excited sweating was next studied. Reflex thermal sweating of the forearm was induced by heating the feet and legs for 20–30 min. DHO and Priscol, in concentrations which had been found to inhibit adrenaline sweating, had no effect on thermal sweating. On the other hand, intradermal atropine (10^{-4} to 10^{-6}) completely suppressed thermal sweating at the site of injection. Mental (emotional) sweating of the palms and soles was separately investigated in five normal and two hyperhidrotic subjects. Again secretion was found to be completely suppressed by local injection or iontophoresis of atropine, while adrenaline blocking agents had no such inhibitory effect.

Profuse sweating commonly occurs during attacks of hypoglycaemia. An opportunity arose to study the effect of atropine on this form of sweating in a patient undergoing an insulin tolerance test. 0·2 ml. of 10^{-4} atropine was injected intradermally in the subclavicular region, and a few minutes later the patient received an intravenous injection of insulin (0·1 unit/kg.). Generalized sweating soon appeared, but the area treated with atropine remained dry.

DISCUSSION

The sweat response to locally injected adrenaline is not inhibited by atropine. Therefore the complete suppression of nervously excited sweating by atropine very strongly suggests that in man all the nerve fibres which control sweating are cholinergic. This conclusion is supported by the finding that adrenaline-blocking

agents, in concentrations which inhibit adrenaline sweating, do not prevent or diminish nervously excited sweating.

It was the observation that palmar sweating was suppressed by dibenamine which originally led Haimovici (1948, 1950) to suggest that human sweat glands were controlled by adrenergic as well as cholinergic nerves. But since the drug was given intravenously, and not locally, the anhidrotic effect may have been due to a central depressant action, similar to that of thiopentone in essential hyperhidrosis (Boyd & Jepson, 1950). It seems most unlikely that dibenamine had any peripheral blocking effect on the sweating mechanism in view of the profuse sweating noted in those individuals who vomited after the infusion. Therefore these observations provide no support for the concept of an adrenergic component in the nervous control of sweating.

There has been some confusion about the response of the palmar sweat glands to adrenaline. Elliott (1905) injected adrenaline into the palmar skin in one subject and observed no increase in local sweat gland activity. Sonnenschein *et al.* (1949) reported no response in the palms in eleven of twelve subjects. Unless spontaneous secretion is first eliminated by nerve block, it may be difficult to evaluate responses in the palm. The effect of vasoconstriction in reducing the amount of secretion might well lead to the sudomotor effect of adrenaline being overlooked. Our results in subjects in whom the median nerve was blocked at the wrist show that the palmar sweat glands resemble the forearm glands in responding to both adrenaline and acetylcholine.

The secretory effect of adrenaline does not appear to be due merely to expression of sweat from the ducts by stimulation of smooth muscle elements, since secretion may continue for over an hour. Nor can it be due to release of acetylcholine from the nerve endings, since it is not inhibited by atropine. Too much significance should not be attributed to the failure of intravenous and intra-arterial adrenaline to elicit sweating: our experience has been that acetylcholine and mecholyl may also produce little or no sweat response when given systemically. The possibility that under certain conditions sweating might be caused by circulating adrenaline has not been excluded. It has been shown, however, that this is not the mechanism of sweating in insulin hypoglycaemia. Similar observations would be of interest in cases of phaeochromocytoma, since a pilomotor reaction sometimes accompanies the paroxysms of hypertension.

In conclusion, we may state that there is no evidence for any adrenergic innervation of human sweat glands. Our results support the view that the nerve supply is solely cholinergic, as shown by Dale & Feldberg in the cat.

SUMMARY

1. It has been confirmed that intradermal injection of adrenaline or noradrenaline usually induces sweating in the skin of the palm or forearm in man.

2. This response is prevented by prior injection (locally) of adrenaline-blocking agents such as dihydroergotamine, dihydroergocristine, dibenamine and tolazoline, but not by atropine.

3. Locally introduced adrenaline-blocking agents do not prevent thermal sweating in the forearm or mental sweating in the palms. Atropine inhibits both types of sweating.

4. There is no evidence that the secretory response of human sweat glands to adrenaline has any physiological significance.

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